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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
01/10/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/563,011	SCHAACK ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *6,8,16,22,23 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-15,17-21,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group II, claims 1-15, 17-21, 24 and 25, in the reply filed on October 24, 2007 is acknowledged. The traversal is on the ground(s) that the claims are directed to small interfering RNAs (siRNAs) targeted to a transcript of a CK2 protein kinase subunit of a mammal which includes a human and a mouse species. Applicants cite the examples showing siRNAs that target both the murine and human CK2 protein kinases. Applicants further argue that the alternatives are directed to an art recognized class of compounds and have a common activity. This is not found persuasive because while some siRNAs may target both genes if complementary to regions of homology between the murine and human species, these siRNAs do not share a special technical feature because they are nevertheless targeted to two distinct genes, no evidence has been provided to demonstrate that all siRNAs targeted to murine CK2 will also inhibit expression of human CK2.

Applicants additionally argue that the special technical feature of groups 1 to 8 is novel and non-obvious over the prior art cited in the restriction requirement. These arguments are not addressed because even if the claims are novel and non-obvious over these references, the inventions still do not make a contribution over the prior art as evidenced by the art rejections that follow

Applicants further argue that it has not been shown that a burden exists in searching the claims of the eight groups, citing MPEP 803. Applicants are correct that

search burden was not addressed in the restriction requirement, however, this restriction is based on lack of unity practice and search burden is not a consideration.

The requirement is still deemed proper and is therefore made FINAL.

Claims 16, 22, 23 and 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and claims 6 and 8 are withdrawn from further consideration as being directed to nonelected nucleotide sequences, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 24, 2007.

Information Disclosure Statement

The information disclosure statement filed March 15, 2006 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each reference that is not in the English language. It has been placed in the application file, but the information referred to in the Buchou et al. reference has not been considered.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claim 21 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 17 is directed to a composition comprising a double stranded oligonucleotide; claim 21, however, broadens rather than limits claim 17 because it is directed to precursors or vectors in addition to the oligonucleotide.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and by dependence claims 2-5, 7, 9-15, 17-21, 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 refers to several gene sequences that are identified by reference to a database accession number. Identification of a gene or protein by accession number renders the claims indefinite because database records identified by such numbers change as new information is added. It is unknown whether a record identified by accession number will remain constant through the term of a patent and thus the metes and bounds of the claim cannot be determined. This rejection may be overcome by providing a formal sequence listing in compliance with the provisions of 37 CFR 1.821-

1825 containing the sequences that were present in these records at the time of filing and incorporating the appropriate sequence identifier into the claim.

Claim 1 is also indefinite because clause a) recites "an oligonucleotide which inhibits expression in cell culture, at a concentration of between 1 and 200 nM, preferably less than 20 nM". The use of the phrase "preferably less than 20nM" renders the claim indefinite because a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation of a concentration of 1-200 nM, and the claim also recites "preferably less than 20 nM" which is the narrower statement of the range/limitation.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim recites the limitation "said sequence" in line 2. There is insufficient antecedent basis for this limitation in the claim because claim 1

recites two strands, each of which has a sequence of 17-21 ribonucleotides, and further refers to the RNA sequence of the sense strand.

Claims 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of these claims recites the limitation "said oligonucleotide, precursor or vector" in line 2. There is insufficient antecedent basis for this limitation in the claims because no precursors or vectors are recited in claim 17.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim is directed to a mixture of oligonucleotides, precursors or vectors and further recites "in particular a mixture comprising at least one oligonucleotide specific for the α subunit, at least one oligonucleotide specific for the α' subunit and at least one oligonucleotide specific for the β subunit." The phrase "in particular" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 9 and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Wyatt (US 6,440, 738).

Claims 9 and 11 refer to claim 1 and are directed to a single stranded oligonucleotide that is the antisense strand of a double stranded oligonucleotide targeted to casein kinase 2 or a precursor oligonucleotide of a double stranded oligonucleotide that includes a single stranded antisense oligonucleotide. The double stranded oligonucleotides of claim 1, which claim 9 claims a portion of, are defined as including "a fragment corresponding to an oligonucleotide which inhibits more than 80% of the expression of the corresponding subunit in cell culture at a concentration of between 1 and 200 nM." While this phrase refers to the sense strand of a siRNA oligonucleotide, it is defined as "corresponding" to a sequence that inhibits expression. Since oligonucleotides that inhibit expression are generally recognized as being complementary to the target gene, this phrase is interpreted to define the sense strand of a siRNA in terms of the behavior of the antisense strand. Since claims 9 and 11 are directed to the antisense portion of a siRNA, the claims are interpreted as any antisense oligonucleotide that inhibits expression by more than 80%.

Wyatt discloses antisense oligonucleotides targeted to the β-subunit of casein kinase 2 that is represented by SEQ ID NOs: 3 and 17. Wyatt discloses in table 1 several oligonucleotides that inhibit expression of casein kinase 2 by at least 80%.

Thus, Wyatt discloses all limitations of and anticipates claims 9 and 11.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt as applied to claims 9 and 11 above, and further in view of Noonberg et al. (US 5,624,803).

Claims 9 and 11 are described in the 102 rejection over Wyatt. Claims 12-14 are directed to expression cassettes and vectors comprising the precursor of claim 11.

Wyatt teaches antisense oligonucleotides targeted to the β-subunit of human casein kinase 2 that is represented by SEQ ID NOs: 3 and 17. Wyatt discloses in table 1 several oligonucleotides that inhibit expression of casein kinase 2 by at least 80%.

Wyatt does not teach human casein kinase 2 beta antisense oligonucleotides that are present in an expression cassette.

Noonberg et al. teach *in vivo* oligonucleotide generators that are useful for producing antisense, ribozymes and triple helix molecules in cells for the purpose of gene regulation. At column 17, lines 2-13, Noonberg et al. teach the vectors of their invention can be administered to cells using techniques known in the art of gene therapy, including administration in liposomes or localized injection. This column provides a teaching of some means for inserting vectors into cells that are known in the art prior to the time of invention.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the antisense oligonucleotides taught by Wyatt by inserting them into the vectors and means for inserting vectors into cell taught by Noonberg et al. Noonberg et al. provide a motivation and reasonable expectation of success in using vectors to produce antisense oligonucleotides by teaching at column 7, lines 26-32 by teaching that such vectors produce oligonucleotides intracellularly in high yield and by actually making such vectors and demonstrating their successful use in producing oligonucleotides.

Thus, the invention of claims 9 and 11-14 would have been obvious, as a whole, at the time of invention.

Claims 1, 3-5, 7, 9-15, 17-21, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt (US 6,440, 738) in view of Bass (Nature 2001, vol. 411, pages 428-429) and Fosnaugh et al. (US 2003/014732).

The claims are directed to double stranded complementary oligonucleotides of 17-21 nucleotides that are targeted to human casein kinase 2. In specific embodiments, the strands comprise 5' phosphate groups, have 3' overhangs of tt or aa, are 19-20 or 21-23 nucleotides in length, are present in expression cassettes, vectors or cells, or are formulated as mixtures of oligonucleotides. In other embodiments, siRNAs are combined in compositions with chemotherapeutic or antiviral agents.

Wyatt teaches antisense oligonucleotides targeted to the β-subunit of human casein kinase 2 that is represented by SEQ ID NOs: 3 and 17. Wyatt discloses in table 1 several oligonucleotides that inhibit expression of casein kinase 2 by at least 80%. Wyatt teaches at column 2 that human casein kinase 2 expression is involved in several types of cancer and in viral replication. At columns 27-28 Wyatt teaches that pharmaceutical compositions of antisense oligonucleotides can be combined with either chemotherapeutic or antiviral agents. Wyatt does not teach siRNAs targeted to the β-subunit of human casein kinase 2.

Bass teaches on page 429, first column, that RNA interference is a routinely used gene silencing technique that has proven to be more robust than antisense techniques by working more often, decreasing expression to lower levels than antisense oligonucleotides and working at concentrations several orders of magnitude below the concentrations typically used in antisense experiments. Bass further teaches in the same column that the discovery of short interfering RNAs that are functional in mammalian cells will inspire further research studies aimed at optimizing the use of siRNAs, as well as at understanding why conventional RNAi using longer dsRNA works in eggs and embryos. Bass speculates that, based on the huge impact the RNAi

technique has had in studies of non-mammalian systems, use of siRNA in mammalian cells could be just as far-reaching, with applications extending to functional genomics and therapeutics.

Fosnaugh et al. teach that siRNAs are made of a sense and antisense strand and are useful for a variety of therapeutic, diagnostic, agricultural, target validation, genomic discovery, genetic engineering and pharmacogenomic applications. Chemically-modified siRNAs are expected to improve various properties of siRNAs including increased *in vivo* nuclease resistance and/or improved cellular uptake. Specific embodiments of siRNAs and chemically modified siRNAs are taught in the figures and at pages 3-8, including 5' phosphate groups at paragraph 46, 3' overhangs at paragraph 17 and lengths of siRNAs of 19-25 nucleotides at paragraph 33. Figure 4 teaches the specific embodiment of tt overhangs. Paragraph 25 teaches expression vectors and cells comprising siRNAs. Paragraphs 195-200 teach siRNA compositions comprising formulations that allow cellular penetration and targeting of specific tissues or organs. In example 3, Fosnaugh et al. teach production of pools of siRNAs. Fosnaugh et al. is considered to comprise a detailed blueprint for how to make and use inhibitory siRNAs to target any known gene.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make siRNAs targeted to the β subunit of human casein kinase 2 and to produce these siRNAs with 3' overhangs, 5' phosphates and stabilizing modifications as taught by Fosnaugh et al. One of ordinary skill in the art would have had a motivation to make siRNAs targeted to casein kinase 2 because Wyatt teaches the role of casein kinase 2 in cancers and viral replication and antisense

oligonucleotides targeted to this gene are useful in inhibiting expression and because Bass teaches that inhibition of gene expression using siRNAs has the advantages of working more often, decreasing expression to lower levels than antisense oligonucleotides and working at concentrations several orders of magnitude below the concentrations typically used in antisense experiments. One of ordinary skill in the art would have had a motivation to make these siRNAs with the features recited in the instant claims because Fosnaugh et al. explicitly teach the advantages of siRNAs having these characteristics. Based on the suggestion of Wyatt that inhibitors of casein kinase 2 be combined with additional chemotherapeutic or antiviral agents, one of ordinary skill in the art would also combine siRNAs targeted to casein kinase 2 with these agents. One of ordinary skill in the art would have had a reasonable expectation of success in producing human casein kinase 2 siRNAs with 3' overhangs, 5' phosphates and stabilizing modifications because synthesis of nucleic acids containing modified nucleotides is routine and well-known in the art.

Thus, the invention of claims 1, 3-5, 7, 9-15, 17-21, 24 and 25 would have been obvious, as a whole, at the time the invention was made.

Claims 1, 3-5, 7, 9-15, 17-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over John et al. (US 2004/0023855) in view of Fosnaugh et al. (US 2003/0143732).

The claims are directed to double stranded complementary oligonucleotides of 17-21 nucleotides that are targeted to human casein kinase 2. In specific embodiments,

the strands comprise 5' phosphate groups, have 3' overhangs of tt or aa, are 19-20 or 21-23 nucleotides in length, are present in expression cassettes, vectors or cells, or are formulated as mixtures of oligonucleotides.

John et al. teach nanoparticles suitable for delivery of therapeutic agents to cells and exemplify this with antisense oligonucleotides targeted to human casein kinase 2. At paragraph 127 John et al. teach that siRNAs have the advantage of being easy to design and can be based on any portion of a messenger RNA molecule. John et al. explicitly suggest the casein kinase 2 mRNA transcript be used to prepare a siRNA molecule. John et al. suggest making siRNAs targeted to human casein kinase 2 but do not produce siRNAs having overhangs, 5' phosphates or stabilizing modifications.

Fosnaugh et al. teach that siRNAs are made of a sense and antisense strand and are useful for a variety of therapeutic, diagnostic, agricultural, target validation, genomic discovery, genetic engineering and pharmacogenomic applications. Chemically-modified siRNAs are expected to improve various properties of siRNAs including increased *in vivo* nuclease resistance and/or improved cellular uptake. Specific embodiments of siRNAs and chemically modified siRNAs are taught in the figures and at pages 3-8, including 5' phosphate groups at paragraph 46, 3' overhangs at paragraph 17 and lengths of siRNAs of 19-25 nucleotides at paragraph 33. Figure 4 teaches the specific embodiment of tt overhangs. Fosnaugh et al. is also considered to comprise a detailed blueprint for how to make and use inhibitory siRNAs to target any known gene. Paragraph 25 teaches expression vectors and cells comprising siRNAs. Paragraphs 195-200 teach siRNA compositions comprising formulations that allow cellular penetration and targeting of specific tissues or organs.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce siRNAs targeted to casein kinase 2 mRNA as suggested by John et al. with 3' overhangs, 5' phosphates and stabilizing modifications as taught by Fosnaugh et al. John et al. provide a motivation to make siRNAs targeted to human casein kinase 2 by explicitly suggesting they be produced and one of ordinary skill in the art would have been motivated to produce such siRNAs with the features recited in the instant claims because Fosnaugh et al. explicitly teach the advantages of siRNAs having these characteristics. One of ordinary skill in the art would have had a reasonable expectation of success in producing human casein kinase 2 siRNAs with 3' overhangs, 5' phosphates and stabilizing modifications because synthesis of nucleic acids containing modified nucleotides is routine and well-known in the art.

Thus, the invention of claims 1, 3-5, 7, 9-15, 17-19 and 21 would have been obvious, as a whole, at the time the invention was made.

Allowable Subject Matter

SEQ ID NO: 26 is free of the prior art searched.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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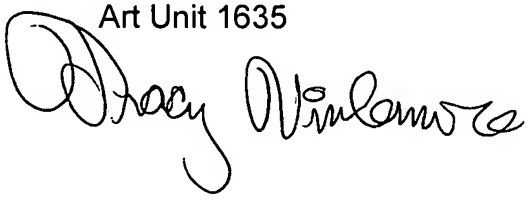
Tracy Vivlemore
Examiner
Art Unit 1635



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